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EXAMINER	
LEE, JAE W	

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
09/17/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/517,225	ALESSI ET AL.	
	Examiner	Art Unit	
	JAE W. LEE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 May 2008* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/16/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

The preliminary amendment to claims, filed on 07/01/2009, is acknowledged, wherein Applicants have canceled claims 19-42.

Claims 1-18 are pending in this application.

Priority

The instant application is the 371 national stage entry of PCT/US03/02509, filed on 01/28/2003 as requested in the declaration. The Examiner notes that the requirements of national stage entry of the instant application had been completed (note assigned U.S. filing date) within 30 months of the earliest claimed priority date; the related international application includes both a search report and a preliminary examination report.

Election

Applicant's election without traverse of Group I, Claims 1-13 and 15-18 in the response filed on 07/01/2009, is acknowledged.

Claim 14 is withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one

or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

Applicants' filing of information disclosure, filed on 04/16/2008, is acknowledged. Those references considered have been initialed, while those missing references or having no date have been lined through.

Objections to the Specification

The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. 606.01). The Examiner suggests ---A method for designing a compound based on the three dimensional structure of phosphoinositide dependent protein kinase 1 (PDK1)---.

The abstract is objected to because it should appear on a separate sheet, see 37 CFR 1.72 (b). Further, the abstract contains a legal phraseology, i.e., said, and exceeds 150 words. See MPEP 608.01 (b).

Applicant is reminded of the proper language and format for an abstract of the disclosure. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract

on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, Applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly page 2, lines 21 and 22; page 9, lines 23, 26 and 29; page 10, lines 1, 5 and 9; Table 2

on pages 16-17; page 19, lines 19-14, 26, 28 and 30; page 22, lines 12-15 and 21; page 42, line 19; page 43, line 4; page 47, line 9; page 54, line 10; page 56, lines 7-9; page 59, lines 4, 9-10 and 22; page 250, line 2; Figures 3, 5 and 7 of the Drawings containing amino acid sequences, and therefore, those sequences should be represented by proper sequence identifier numbers. Also, see particularly Examples 2, 3, 4 and 7 on pages 69, 114, 159 and 268, respectively of the specification containing a list of atomic coordinates representing the disclosure of an amino acid sequence, and therefore the Table should have a heading identifying the amino acid sequence in the Examples 2, 3, 4 and 7.

The specification is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 14, line 14; and page 61, line 8. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Claim Objections

Claims 3, 4, are objected to because of the following informalities:

Claims 3 and 4 are objected to for improperly broadening the scope of the claims which they depend from. Claim 1 specifically recites that the three-dimensional structure is one that is determined for a polypeptide *consisting of residues 51 to 359 of full length human PDK1* (emphasis added). However, Claims 3 and 4 add 2 and 20

additional amino acid residues, respectively, which is improper. The Examiner suggests re-writing these claims as an independent claim.

Claim 9 is objected to for the recitation of “2, 3 or 4, or 7 or 8” with can be substantially improved with respect to form. The Examiner suggests replacing the noted phrase with ---2, 3, 4, 7 or 8---. In the interest of advancing prosecution, the noted phrase is interpreted as suggested by the Examiner.

Claims 11-13 are objected to because the recitation of “PKB”, “PH”, “SGK”, “S6K”, and “PIF” should be in parenthesis and follow the phrase it abbreviates when used for the first time in a claim.

Claim 12 is objected to for reciting a peptide sequence, “FXXFS/TY”, which fails to comply with the sequence rules as set forth in 37 CFR 1.821(a)(1) and (a)(2). The Examiner suggests inserting a SEQ ID NO corresponding to said peptide sequence.

Claim 13 is objected to for the recitations of “with the said hydrophobic”, “of the said phosphate binding pocket" and “with the said phosphate binding pocket" in lines 8, 10 and 13, respectively, which can be substantially improved with respect to grammar. The Examiner suggests deletion of either "the" or "said".

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

It is noted by the Examiner that although claims 1 and 13 recite the phrase, “means to”, this does not invoke 35 U.S.C. 112, sixth paragraph because the claim does not include the phrase “means for” or “step for” according to MPEP § 2181.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13 and 15-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 13 recite the phrase, "modelling means", which is unclear and indefinite. It is noted by the Examiner that the specification does not define this phrase, and as such, it is unclear what the scope of this phrase is.

Claims 1, 10 and 13 recite the phrases, "residues equivalent to", “equivalent residues" or “position equivalent to” which is unclear and indefinite. It is unclear with as to what is considered “equivalent”. Should any similar residues or similar positions be regarded as being encompassed by "equivalent" or do Applicants intend to mean "identical"? It is suggested that Applicants clarify the meaning of the noted phrases.

Claims 13 and 15 recite the phrase “hydrophobic pocket” which is unclear and indefinite. It is unclear with respect to which hydrophobic residues should be regarded as being in the “hydrophobic pocket". It is suggested that Applicants clarify the meaning of the noted phrases.

Claims 1-4 recite “(or part thereof)”, which is unclear and indefinite. It is unclear respect to whether or not the recitation inside the parenthesis should be considered as a claim limitation or not. In the interest of advancing prosecution, the noted phrase is interpreted as "or part thereof" WITHOUT the parenthesis.

Claims 1-4, 10, 13 recite specific amino acid positions, i.e., “residues 51 to 359 of full length human PDK1”, “Met51”, “residues 71 to 359 of full length human PDK1”, “Lys115, Ile118…Leu155 on β-sheet 5”, “Lys76, Arg131, Thr148, and Gln150”, or “residues equivalent to 123-136”, “Lys114, Ile118, Ile119…Leu155” which are unclear and indefinite. It is unclear because there is a lack of nexus between the recited positions, and a specific amino acid sequence, i.e., SEQ ID NO: 1, which the recited positions are referring to. The Examiner suggests inserting a corresponding SEQ ID NOs. In the interest of advancing prosecution, the noted phrases are interpreted as any amino acid residues.

Claim 9 recites the phrase, "*represented by* the structure co-ordinates shown in Examples…", which is unclear and indefinite (emphasis added). The reason is that it is unclear whether the phrase following "represented by" should be regarded as a claim limitation or not. In the interest of advancing prosecution, the noted phrase is not given any patentable weight.

Claims 10 recites the phrases inside parenthesis, “(formed by residues including residues Lys115, Ile118, Ile119 on the αB helix, Val124, Val127 on the αC helix and Leu 155 on ~3-sheet 5 of full length human PDK1, or equivalent residues),” “(formed by residues including residues Lys76, Arg 131, Thr 148 and Glnl50 of full length human PDK1, or equivalent residues)” and “(residues equivalent to 123-136 of full length human PDK1),” which are unclear and indefinite. It is unclear respect to whether or not the recitations inside the parenthesis should be considered as a claim limitation or not.

In the interest of advancing prosecution, the noted phrases are interpreted WITHOUT the parenthesis.

Claim 11 recites the phrase, “other PH-domain” which is unclear and indefinite. It is unclear with regard to what “other PH-domain” encompasses. In the interest of advancing prosecution, the noted phrase is not given any patentable weight.

Claim 12 recites the phrase, “*other substrate* of PDK1", which is unclear and indefinite (emphasis added). It is unclear with regard to what “*other substrate* of PDK1” encompasses. In the interest of advancing prosecution, the noted phrase is not given any patentable weight.

Claim 13 recites the phrase, “(PIF binding protein)”, which is unclear and indefinite. It is unclear respect to whether or not the recitations inside the parenthesis should be considered as a claim limitation or not. If one interprets "(PIF binding protein)” as "for example, PIF binding protein," it renders the claim indefinite because it is unclear whether the limitation inside the parenthesis is part of the claimed invention or not. See MPEP § 2173.05(d). In the interest of advancing prosecution, the noted phrase is not given any patentable weight.

Claim 17 recites the phrase "principle component analysis" which is unclear and indefinite. It is unclear what kind of analysis this is. In the interest of advancing prosecution, the noted phrase is not given any patentable weight.

Claim 18 recites the phrase, “open”, “closed” or “intermediate”, which is unclear and indefinite. Since there is no *reference* activation state from which other “open”, “closed” or “intermediate” state can be compared to, it is unclear what is considered

"open", "closed" or "intermediate". In the interest of advancing prosecution, this claim is not given any patentable weight.

Claims 1-13 and 15-18 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Since claims 1, 13 and 17 (all other claims dependent therefrom) recite that the instant methods are for selecting a compound that 'modulates the activity of a protein kinase' or 'assessing the activation state of a protein kinase', it is apparent that the omitted steps are those that enable one of skill in the art to determine the activity of a protein kinase or the activation state of a protein kinase, i.e., "wet" biochemical assays including but not limited to kinase assays, and fluorescence resonance energy transfer (FRET) to determine various 3-D conformations, i.e., "open", or "closed" state, of a protein kinase.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 and 15-18 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to [i] a method for selecting or designing a compound for modulating the activity of phosphoinositide dependent protein kinase 1 (PDK1), the method comprising the step of using molecular modelling means to select or design a compound that is predicted to interact with the protein kinase catalytic domain of PDK1, wherein a three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 is compared with a three-dimensional structure of a compound, and a compound that is predicted to interact with the said protein kinase catalytic domain is selected, wherein the three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 is a three-dimensional structure or part thereof determined for a polypeptide consisting of residues equivalent to any residues of full length human PDK1, or a fragment or fusion thereof, optionally, wherein the three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 structure is obtainable by X-ray analysis of a crystal obtainable using a mother liquor solution comprising ammonium sulphate; [ii] a method for selecting or designing a compound for modulating the activity of a hydrophobic pocket-containing protein kinase having a hydrophobic pocket in the position equivalent to the hydrophobic pocket of human PDK1 that is defined by any residues of full- length human PDK1 and further having a phosphate binding pocket in the position equivalent to the phosphate binding pocket of human PDK1 that is defined by any residues, the method comprising the step of using molecular modelling means to select or design a compound that is predicted to interact with the said hydrophobic pocket-containing protein kinase, wherein a three-dimensional structure of a compound is compared with a three-dimensional structure of

the said phosphate binding pocket and optionally also the hydrophobic pocket and/or αC helix or region interacting therewith, and a compound that is predicted to interact with the said phosphate binding pocket and optionally also the hydrophobic pocket and/or αC helix or region interacting therewith, is selected; and [iii] a method for assessing the activation state of a structure for a protein kinase, wherein the structure is analysed using the structure co-ordinates. See rejections under 112 2nd paragraph for the claim interpretation.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of [compositions or methods], it must be clear that: (1) the identifying characteristics of the claimed [compositions or methods] have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent

said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (paraphrased from Enzo Biochemical Inc. v. Gen-Probe Inc. (CAFC (2002) 63 USPQ2d 1609).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both Lily and Enzo Biochemical to methods of using products, wherein said products lack adequate written description. While in University of Rochester v. G.D. Searle & Co. the methods were held to lack written description because not a single example of the product used in the claimed methods was described, the same analysis applies wherein the product, used in the claimed methods, must have adequate written description as noted from Enzo Biochemical (see above).

The scope of claims 1-13 and 15-18 are so broad as to encompass [i] a method for selecting or designing a compound for modulating the activity of phosphoinositide dependent protein kinase 1 (PDK1), the method comprising the step of using molecular modelling means to select or design a compound that is predicted to interact with the protein kinase catalytic domain of PDK1, wherein *a genus of three-dimensional structure of any* part of the protein kinase catalytic domain of PDK1 is compared with a three-dimensional structure of a compound, and a compound that is predicted to interact with the said protein kinase catalytic domain is selected, wherein *said genus of*

three-dimensional structures of any part of the protein kinase catalytic domain of PDK1 is *any three-dimensional structure or part thereof, including any homology models,* determined for *any polypeptide consisting of residues equivalent to any residues of full length human PDK1, or a fragment or fusion thereof*, optionally, wherein the genus of three-dimensional structures of any part of the protein kinase catalytic domain of PDK1 structure is obtainable by X-ray analysis of a crystal obtainable using a mother liquor solution comprising ammonium sulphate; [ii] a method for selecting or designing a compound for modulating *any activity of a genus of any hydrophobic pocket-containing protein kinase* having *any hydrophobic pocket in the position equivalent to* the hydrophobic pocket of human PDK1 that is defined by *any residues of full-length human PDK1* and further having *any phosphate binding pocket in the position equivalent to the phosphate binding pocket of human PDK1 that is defined by any residues*, the method comprising the step of using molecular modelling means to select or design a compound that is predicted to interact with *said genus of hydrophobic pocket-containing protein kinases*, wherein a three-dimensional structure of a compound is compared with *a genus of three-dimensional structures, including any homology models, of said phosphate binding pocket* and optionally also *the genus of hydrophobic pockets and/or a genus of αC helixes or a genus of any region interacting therewith*, and a compound that is predicted to interact with said phosphate binding pocket and optionally also the hydrophobic pocket and/or αC helix or region interacting therewith, is selected; and [iii] a method for assessing the activation state of *a genus of structures for any protein*

kinase, including any homology models, wherein the structure is analysed using *any structure co-ordinates* (italicized for added emphasis).

However, given [A] the high level of unpredictability associated with making a crystalline protein with an expectation that it is an X-ray diffraction-quality protein crystal, [B] the fact that a singular chemical composition can crystallize differently based on the crystallization conditions, [C] the space group and unit cell dimensions of a crystal of any given chemical composition can only be determined by analyzing that the crystal's X-ray diffraction data (Giege *et al*. Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., 1994, D50: 339-350), [D] the high level of unpredictability associated with the use of any homology models, that can be generated from the data generated for use in rational drug design as recited in steps of claims 1-13 and 15-18, as acknowledged by Lambert et al., "[p]otential or existent homology models cannot provide the necessary degree of specificity" in the in silico design of modulators (see p. 3, ¶[0017] of Lambert et al., US Patent Application Publication 2004/0137518), and [E] the limited disclosure of the specification which provides only a single method of crystallizing a human PDK1 protein consisting of the residues 51-359, which forms in space group $P3_221$, with unit cell dimensions a = 123.01 Å, b = 123.01 Å, c = 47.62 Å, $\alpha = \beta = \gamma = 90°$ (see pages 57 and 61 of the specification), and a single method of performing rationale drug design based on the 3-D structure of the PDK1 protein defined by the atomic coordinates of Example 2, 3, 4, 7 or 8 (see pages 69-352 of the specification), one of skill in the art would not have recognized that Applicants were in possession of the recited genus of methods of

performing rationale drug design based on [i] *any homology models of the genus of PDK1 proteins including any fragments or fusions thereof* that can be generated from the use of *any atomic coordinates of any equivalent residues;* [ii] *any homology models of the genus of any hydrophobic pocket-containing protein kinases* that can be generated from the use of *any atomic coordinates of any equivalent residues;* or [iii] a method for assessing the activation state of *any structure including any homology models for any protein kinase, wherein said structure is analysed using any structure coordinates* (emphasis added, and also see further discussion regarding the "unpredictability of making protein crystals" and the "use of homology models" under 112 1st paragraph enablement rejection below). In addition, there is no disclosure of any particular relationship between the structures of the crystallized [i] genus of PDK1 proteins including any fragments or fusions thereof, [ii] genus of hydrophobic pocket-containing protein kinases, and [iii] genus of protein kinases, and the crystallization conditions. Also, the specification fails to describe additional representative species of the crystallized [i] genus of PDK1 proteins including any fragments or fusions thereof, [ii] genus of hydrophobic pocket-containing protein kinases, and [iii] genus of protein kinases required to obtain the various diffraction patterns or atomic coordinates by any identifying structural characteristics or properties other than those in Examples 2-4, 7 and 8. In general, for the genus of methods for crystallizing a protein, and methods of performing rationale drug design, to be adequately described, the following must be disclosed: (1) the composition of the crystal (exact structural features of all molecules in the crystal must be described, i.e., the protein (preferably a SEQ ID NO of all included

residues), (2) the space group, (3) the unit cell dimensions of the crystal, and (4) the atomic coordinates which defines the 3-D structure of the crystallized protein.

Given the lack of additional representative species of the genus of methods as described above, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-13 and 15-18 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method for selecting or designing a compound for modulating the kinase activity of human PDK1, said method comprising the step of performing rationale drug design based on the 3-D structure of the PDK1 protein defined by the atomic coordinates of Example 2, 3, 4, 7 or 8, wherein said atomic coordinates are obtained from an X-ray diffraction analysis of a crystalline human PDK1 protein consisting of the residues 51-359, which forms in space group $P3_221$, with unit cell dimensions a = 123.01 Å, b = 123.01 Å, c = 47.62 Å, $\alpha = \beta = \gamma = 90°$, does not reasonably provide enablement for [i] any method for selecting or designing a compound for modulating the activity of phosphoinositide dependent protein kinase 1 (PDK1), the method comprising the step of using molecular modelling means to select or design a compound that is predicted to interact with the protein kinase

catalytic domain of PDK1, wherein a three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 is compared with a three-dimensional structure of a compound, and a compound that is predicted to interact with the said protein kinase catalytic domain is selected, wherein the three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 is a three-dimensional structure or part thereof determined for a polypeptide consisting of residues equivalent to any residues of full length human PDK1, or a fragment or fusion thereof, optionally, wherein the three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 structure is obtainable by X-ray analysis of a crystal obtainable using a mother liquor solution comprising ammonium sulphate; [ii] any method for selecting or designing a compound for modulating the activity of a hydrophobic pocket-containing protein kinase having a hydrophobic pocket in the position equivalent to the hydrophobic pocket of human PDK1 that is defined by any residues of full- length human PDK1 and further having a phosphate binding pocket in the position equivalent to the phosphate binding pocket of human PDK1 that is defined by any residues, the method comprising the step of using molecular modelling means to select or design a compound that is predicted to interact with the said hydrophobic pocket-containing protein kinase, wherein a three-dimensional structure of a compound is compared with a three-dimensional structure of the said phosphate binding pocket and optionally also the hydrophobic pocket and/or αC helix or region interacting therewith, and a compound that is predicted to interact with the said phosphate binding pocket and optionally also the hydrophobic pocket and/or αC helix or region interacting therewith, is selected; and [iii] any method for

assessing the activation state of a structure for a protein kinase, wherein the structure is analysed using the structure co-ordinates. See above 112 2nd paragraph rejections for the claim interpretation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. To practice the claimed methods to the full extent of their scope would require undue experimentation.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands (858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims, (B) The nature of the invention, (C) The state of the prior art; (D) The level of one of ordinary skill, (E) The level of predictability in the art; (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See M.P.E.P. § 2164. 01(a). The factors most relevant to the instant rejection are addressed in detail below.

(A) The breadth of the claims: The scope of claims 1-13 and 15-18 are so broad as to encompass [i] a method for selecting or designing a compound for modulating the activity of phosphoinositide dependent protein kinase 1 (PDK1), the method comprising the step of using molecular modelling means to select or design a compound that is predicted to interact with the protein kinase catalytic domain of PDK1, wherein *a genus of three-dimensional structure of any* part of the protein kinase catalytic domain of PDK1 is compared with a three-dimensional structure of a compound, and a compound that is

predicted to interact with the said protein kinase catalytic domain is selected, wherein *said genus of three-dimensional structures of any* part of the protein kinase catalytic domain of PDK1 is *any three-dimensional structure or part thereof, including any homology models,* determined for *any polypeptide consisting of residues equivalent to any residues of full length human PDK1, or a fragment or fusion thereof*, optionally, wherein the genus of three-dimensional structures of any part of the protein kinase catalytic domain of PDK1 structure is obtainable by X-ray analysis of a crystal obtainable using a mother liquor solution comprising ammonium sulphate; [ii] a method for selecting or designing a compound for modulating *any activity of a genus of any hydrophobic pocket-containing protein kinase* having *any hydrophobic pocket in the position equivalent to* the hydrophobic pocket of human PDK1 that is defined by *any residues of full-length human PDK1* and further having *any phosphate binding pocket in the position equivalent to the phosphate binding pocket of human PDK1 that is defined by any residues*, the method comprising the step of using molecular modelling means to select or design a compound that is predicted to interact with *said genus of hydrophobic pocket-containing protein kinases*, wherein a three-dimensional structure of a compound is compared with *a genus of three-dimensional structures, including any homology models, of said phosphate binding pocket* and optionally also *the genus of hydrophobic pockets and/or a genus of αC helixes or a genus of any region interacting therewith*, and a compound that is predicted to interact with said phosphate binding pocket and optionally also the hydrophobic pocket and/or αC helix or region interacting therewith, is selected; and [iii] a method for assessing the activation state of *a genus of*

structures for any protein kinase, including any homology models, wherein the structure is analysed using *any structure co-ordinates* (italicized for added emphasis). In this case, the specification is enabling for a method for selecting or designing a compound for modulating the kinase activity of human PDK1, said method comprising the step of performing rationale drug design based on the 3-D structure of the PDK1 protein defined by the atomic coordinates of Example 2, 3, 4, 7 or 8, wherein said atomic coordinates are obtained from an X-ray diffraction analysis of a crystalline human PDK1 protein consisting of the residues 51-359, which forms in space group $P3_221$, with unit cell dimensions a = 123.01 Å, b = 123.01 Å, c = 47.62 Å, $\alpha = \beta = \gamma = 90°$ (see pages 57, 61 and 69-352 of the specification).

(B) The state of the prior art: The level of one of ordinary skill; and The level of predictability in the art: At the time of the invention, methods of crystallizing a protein to obtain an X-ray diffraction quality crystal having specific unit cell dimensions and space group, and determining the 3-D structure of the protein from the X-ray diffraction analysis of the crystal for the purpose of structure-based drug discovery, were known in the prior art. With regard to this, the state of the art at the time of the invention acknowledges a high level of unpredictability for making and using X-ray diffraction quality protein crystals. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "crystallization is usually quite difficult to achieve" (p. 375) and that "well ordered crystals…are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a

crystal without forming large holes or channels between the individual molecules" (p. 374). Branden et al. further teaches that while there are instances where the structure of a protein has been resolved to a resolution of 1 Å, "only a few small proteins have been determined to such high resolution" (p. 382, first full paragraph). Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "the science of protein crystallization is an underdeveloped area" and "protein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal as evidenced by Kierzek et al. (2001, *Biophys Chem* 91:1-20), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (p. 2, left column, top). Even minor alterations in the crystallization parameters can affect crystallization as evidenced by Branden et al., which teach that the formation of protein crystals is critically dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions and ligands to the protein (page 375, middle). Furthermore, Branden et al. teach that even small changes in the crystallization parameters, *e.g.*, pH, can cause the molecules to pack in different ways to produce different crystal forms (page 375, bottom). In addition, Wiencek (*Ann Rev Biomed Eng,* 1999, 1:505-534) teaches that "protein solubility will change dramatically as pH is altered by ~ 0.5 pH units…some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom).

Regarding the use of "homology models" for rationale drug design, Lambert et al. acknowledges that "[p]otential or existent homology models cannot provide the necessary degree of specificity" in the in silico design of modulators (see p. 3, ¶[0017] of Lambert et al., US Patent Application Publication 2004/0137518). In view of these teachings, a skilled artisan would have recognized that it is highly unpredictable to practice [i] any method for selecting or designing a compound for modulating the activity of phosphoinositide dependent protein kinase 1 (PDK1), the method comprising the step of using molecular modelling means to select or design a compound that is predicted to interact with the protein kinase catalytic domain of PDK1, wherein *any three-dimensional structure of any* part of the protein kinase catalytic domain of PDK1 is compared with a three-dimensional structure of a compound, and a compound that is predicted to interact with the said protein kinase catalytic domain is selected, wherein *any three-dimensional structures of any* part of the protein kinase catalytic domain of PDK1 is *any three-dimensional structure or part thereof, including any homology models,* determined for *any polypeptide consisting of residues equivalent to any residues of full length human PDK1, or a fragment or fusion thereof*, optionally, wherein any three-dimensional structures of any part of the protein kinase catalytic domain of PDK1 structure is obtainable by X-ray analysis of a crystal obtainable using a mother liquor solution comprising ammonium sulphate; [ii] any method for selecting or designing a compound for modulating *any activity of any hydrophobic pocket-containing protein kinase* having *any hydrophobic pocket in the position equivalent to* the hydrophobic pocket of human PDK1 that is defined by *any residues of full-length human*

PDK1 and further having *any phosphate binding pocket in the position equivalent to the phosphate binding pocket of human PDK1 that is defined by any residues*, the method comprising the step of using molecular modelling means to select or design a compound that is predicted to interact with *any hydrophobic pocket-containing protein kinases*, wherein a three-dimensional structure of a compound is compared with *any three-dimensional structures, including any homology models, of said phosphate binding pocket* and optionally also *any hydrophobic pockets and/or any αC helixes or any region interacting therewith*, and a compound that is predicted to interact with said phosphate binding pocket and optionally also the hydrophobic pocket and/or αC helix or region interacting therewith, is selected; and [iii] any method for assessing the activation state of *any structures for any protein kinase, including any homology models,* wherein the structure is analysed using *any structure co-ordinates* (italicized for added emphasis).

(C) The amount of direction provided by the inventor and the existence of working examples: The specification discloses only a single method for selecting or designing a compound for modulating the kinase activity of human PDK1, said method comprising the step of performing rationale drug design based on the 3-D structure of the PDK1 protein defined by the atomic coordinates of Example 2, 3, 4, 7 or 8, wherein said atomic coordinates are obtained from an X-ray diffraction analysis of a crystalline human PDK1 protein consisting of the residues 51-359, which forms in space group $P3_221$, with unit cell dimensions a = 123.01 Å, b = 123.01 Å, c = 47.62 Å, $\alpha = \beta = \gamma = 90°$ (see pages 57, 61 and 69-352 of the specification). The specification fails to disclose

any other methods of [i] selecting or designing a compound for modulating the activity of phosphoinositide dependent protein kinase 1 (PDK1), the method comprising the step of using molecular modelling means to select or design a compound that is predicted to interact with the protein kinase catalytic domain of PDK1, wherein *any three-dimensional structure of any* part of the protein kinase catalytic domain of PDK1 is compared with a three-dimensional structure of a compound, and a compound that is predicted to interact with the said protein kinase catalytic domain is selected, wherein *any three-dimensional structures of any* part of the protein kinase catalytic domain of PDK1 is *any three-dimensional structure or part thereof, including any homology models,* determined for *any polypeptide consisting of residues equivalent to any residues of full length human PDK1, or a fragment or fusion thereof*, optionally, wherein any three-dimensional structures of any part of the protein kinase catalytic domain of PDK1 structure is obtainable by X-ray analysis of a crystal obtainable using a mother liquor solution comprising ammonium sulphate; [ii] selecting or designing a compound for modulating *any activity of any hydrophobic pocket-containing protein kinase* having *any hydrophobic pocket in the position equivalent to* the hydrophobic pocket of human PDK1 that is defined by *any residues of full-length human PDK1* and further having *any phosphate binding pocket in the position equivalent to the phosphate binding pocket of human PDK1 that is defined by any residues*, the method comprising the step of using molecular modelling means to select or design a compound that is predicted to interact with *any hydrophobic pocket-containing protein kinases*, wherein a three-dimensional structure of a compound is compared with *any three-dimensional structures, including*

any homology models, of said phosphate binding pocket and optionally also *any hydrophobic pockets and/or any αC helixes or any region interacting therewith*, and a compound that is predicted to interact with said phosphate binding pocket and optionally also the hydrophobic pocket and/or αC helix or region interacting therewith, is selected; and [iii] assessing the activation state of *any structures for any protein kinase, including any homology models,* wherein the structure is analysed using *any structure co-ordinates,* as encompassed by the claims (italicized for added emphasis).

(D) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of crystallizing a protein to obtain an X-ray diffraction quality crystal having specific unit cell dimensions and space group, and performing rationale drug design based on the 3-D structure defined by the atomic coordinates obtained from an X-ray diffraction analysis of said crystalline protein, were known in the prior art, it was not routine in the art to screen an infinite number of "homology models" that can be generated from the use of *any atomic coordinates* [i] corresponding to *any equivalent residue* of *any PDK1 proteins including any fragments or fusions thereof,* [ii] corresponding to *any equivalent residue* of *any hydrophobic pocket-containing protein kinases;* or [iii] *of any protein kinase*, as encompassed by the claims without guidance as to which of those structures is/are useful in accordance with the asserted utility of the claimed invention, i.e., structure based rationale drug design of therapeutic compounds (see lines 15-16 on page 4 of the specification). In other words, it was not routine in the art for a skilled artisan to determine which 3-D models, out of an infinite number of possible "homology models" that can be generated using the atomic

coordinates [i] corresponding to *any equivalent residue* of *any PDK1 proteins including any fragments or fusions thereof,* [ii] corresponding to *any equivalent residue* of *any hydrophobic pocket-containing protein kinases;* or [iii] *of any protein kinase*, represent biologically relevant 3-D structures of the genus of protein kinases as discussed above including any fragments, fusions, equivalents thereof, so that they can be used for the structure-based rationale drug design.

As such, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement, In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, practicing the scope of the invention as claimed is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17-18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Godden et al. (Evaluation of docking strategies for virtual screening of compound

databases: cAMP-dependent serine/threonine kinase as an example, Journal of Molecular Graphics and Modelling, Volume 16, Issue 3, June 1998, Pages 139-143).

The instant claims are drawn to a method for assessing the activation state of a structure for a protein kinase, wherein the structure is analysed using the structure co-ordinates. See rejections under 112 2nd paragraph for the claim interpretation.

Godden et al. teach a method for analyzing different structural conformations of the 3-D structure of cAMP-dependent serine/threonine kinase when various inhibitors are bound (see page 140, right column under "Structure comparison"). Godden et al. further teach said method comprising assessing the difference between said conformations of the 3-D structure of cAMP-dependent serine/threonine kinase, and the experimentally obtained 3-D structure of cAMP-dependent serine/threonine kinase via X-ray diffraction analysis. Therefore, teachings of Godden et al. anticipate claims 17-18.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13 and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. (The structural basis for specificity of substrate and

recruitment peptides for cyclin-dependent kinases, Nat Cell Biol., 1999, Nov; Vol. 1, No. 7, pp: 438-443) in view of *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983).

Claims are drawn to [i] a method for selecting or designing a compound for modulating the activity of phosphoinositide dependent protein kinase 1 (PDK1), the method comprising the step of using molecular modelling means to select or design a compound that is predicted to interact with the protein kinase catalytic domain of PDK1, wherein a three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 is compared with a three-dimensional structure of a compound, and a compound that is predicted to interact with the said protein kinase catalytic domain is selected, wherein the three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 is a three-dimensional structure or part thereof determined for a polypeptide consisting of residues equivalent to any residues of full length human PDK1, or a fragment or fusion thereof, optionally, wherein the three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 structure is obtainable by X-ray analysis of a crystal obtainable using a mother liquor solution comprising ammonium sulphate; [ii] a method for selecting or designing a compound for modulating the activity of a hydrophobic pocket-containing protein kinase having a hydrophobic pocket in the position equivalent to the hydrophobic pocket of human PDK1 that is defined by any residues of full- length human PDK1 and further having a phosphate binding pocket in the position equivalent to the phosphate binding pocket of human PDK1 that is defined by any residues, the method comprising the step of using molecular modelling means to select or design a compound that is predicted to interact

with the said hydrophobic pocket-containing protein kinase, wherein a three-dimensional structure of a compound is compared with a three-dimensional structure of the said phosphate binding pocket and optionally also the hydrophobic pocket and/or αC helix or region interacting therewith, and a compound that is predicted to interact with the said phosphate binding pocket and optionally also the hydrophobic pocket and/or αC helix or region interacting therewith, is selected; and [iii] a method for assessing the activation state of a structure for a protein kinase, wherein the structure is analysed using the structure co-ordinates. See rejections under 112 2nd paragraph for the claim interpretation.

Brown et al. teach a method comprising (i) purifying recombinant CDK2 protein, which is a serine/threonine kinase; (ii) crystallizing the purified CDK2 protein to obtain an X-ray diffraction quality crystal of the CDK2 protein; (iii) resolving the structure of the crystallized CDK2 protein using x-ray crystallography to obtain X-ray diffraction pattern; (iv) applying the atomic coordinates generated from resolving the structure of the crystallized CDK2 protein to a computer algorithm to generate a 3-D structure of the CDK2 protein suitable for use in designing ligands that will bind to the CDK2 protein active site; and (v) applying an iterative process whereby molecular structures, i.e., cyclin A3 or cyclin A3-$p27^{KIP1}$, are applied to the computer generated model to identify CDK2 binding ligands (see under "Methods" on page 443, and Figures 1-3). Brown et al. further teach synthesizing, and purifying the identified ligand, i.e., HHASPRK (see under "Methods" on page 443). It is noted that CDK2 taught by Brown et al. meet the limitation of claims because the "a three-dimensional structure or a part thereof" used in

the claimed method is that determined for any polypeptide consisting of residues *equivalent to* (emphasis added, see above discussions regarding the scope of claims in 112 1st and 2nd paragraph rejections). It is noted by the Examiner that by virtue of being a kinase, CDK2 inherently possesses "protein kinase catalytic domain", "phosphate binding pocket" and "hydrophobic pocket".

Brown et al. do not teach the atomic coordinates as set forth in Examples 2-4, 7 and 8.

In *Gulack*, the court held that nonfunctional descriptive material in a claim does not distinguish the prior art in terms of patentability. The key factor in analyzing the obviousness of these claims over the prior art is the determination that the machine-readable data storage medium is known and is unmodified. If the difference between the prior art and the claimed invention as a whole is limited to descriptive material stored on or employed by a machine, it is necessary to determine whether the descriptive material is functional descriptive material or nonfunctional descriptive material. In this case, the atomic coordinates as disclosed in Examples 2-4, 7 and 8 are nonfunctional descriptive material and the claimed methods use a known unmodified computer algorithm. Data, disclosed as the atomic coordinates of Examples 2-4, 7 and 8, which are fed into a known algorithm whose purpose is to compare or modify those data using a series of processing steps, do not impose a change in the processing steps and are thus nonfunctional descriptive material. Nonfunctional descriptive material cannot render nonobvious an invention that would have otherwise been obvious.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to practice the method as taught by Brown et al., wherein only nonfunctional descriptive material is additionally present in the claims, which do not distinguish the claimed method from Brown et al. according to *In re Gulack*.

Conclusion

Claims 1-13 and 15-18 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

The instant Office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on M-F between 9:00-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

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/JAE W LEE/
Examiner, Art Unit 1656

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